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(54) Title: THE PREPARATION OF ENANTIOMERICALLY-ENRICHED <i>THREO</i> -METHYLPHENIDATE			
(57) Abstract			
<p>A process for increasing the enantiomeric excess of an enantiomerically-enriched mixture of enantiomers of an acid addition salt of <i>threo</i>-methylphenidate, the acid being achiral, comprises crystallisation from, or partial dissolution in, a solvent; and, if necessary, removing any resolving agent that may be present. This process may be preceded by biocatalytic resolution of racemic <i>threo</i>-methylphenidate or ritalinic acid.</p>			

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THE PREPARATION OF ENANTIOMERICALLY-ENRICHED
THREO-METHYLPHENIDATE

Field of the Invention

This invention relates to processes for the preparation of enantiomerically-enriched
5 *threo*-methylphenidate, and in particular to bioresolution, to the separation of the
enantiomers of acid addition salt forms of *threo*-methylphenidate, and to the enhancement
of enantiomeric excess (ee) of one enantiomer in a mixture.

Background of the Invention

Methylphenidate is a therapeutic agent that is widely used in the treatment of
10 attention-deficient hyperactivity disorder. It is a controlled substance.

Methylphenidate was first prepared as a mixture of the *erythro* and *threo*
racemates. US-A-2957880 discloses studies upon the two racemic mixtures, which
revealed that the therapeutic activity resides in the *threo* diastereoisomer. It is now
considered that it is the *d-threo* [or (*R,R*)] enantiomer that has the preferred therapeutic
15 activity. Uses of this enantiomer are disclosed in WO-A-9703671, WO-A-9703672 and
WO-A-9703673, the contents of which are incorporated herein by reference.

The resolution of methylphenidate has been achieved using the expensive resolving
agent 1,1'-binaphthyl-2,2'-diyl hydrogen phosphate, a process reported by Patrick *et al*,
The Journal of Pharmacology and Experimental Therapeutics, 241:152-158 (1987).
20 Patrick *et al* also disclose a modest improvement in the enantiopurity of *threo*-
methylphenidate hydrochloride, by crystallisation, from 95-97% to 99% ee. It is now
known that the product is contaminated with resolving agent and/or ritalinic acid; see WO-
A-9727176.

WO-A-9727176 and WO-A-9732851 disclose that the resolution of
25 methylphenidate has also been achieved, more economically, using either *O,O'*-
diaroyltartaric acids or menthoxyacetic acid. These resolutions provide *d-threo*-
methylphenidate in high ee and chemical purity, e.g. containing less than 2% w/w of
resolving agent and/or ritalinic acid.

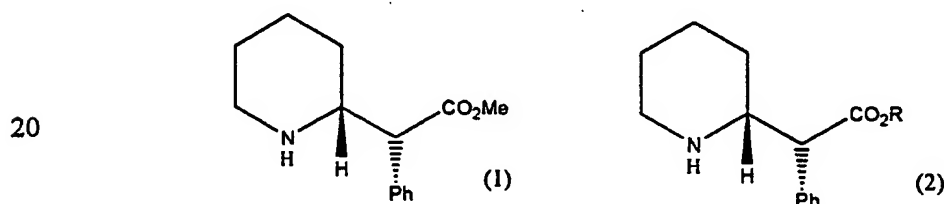
Generally speaking, the racemate and single enantiomers of a salt of a chiral
30 compound such as *threo*-methylphenidate have different solid-state crystalline forms.
Consequently, in solution, such a salt will have an enantiomeric composition which
corresponds to its point of maximum solubility (the eutectic composition), and this is

dependent upon the solubility of the racemic salt and the single enantiomer salt. The solubility ratio α is given by the ratio of the solubility of the racemate salt divided by the solubility of the single enantiomer salt.

Summary of the Invention

5 One aspect of the present invention is based upon the discovery that certain crystalline salts of *threo*-methylphenidate, wherein the counterion is achiral, allow for the enhancement of enantiomeric excess (ee) by recrystallisation/crystallisation of partially enriched material in a suitable solvent. In particular, it has surprisingly been found that, in the case of *threo*-methylphenidate, certain salts of the single enantiomer showed much
10 lower solubility than the corresponding racemate in methanol/TBME (*tert*-butyl methyl ether).

A second aspect of the present invention is based on the discovery that (*R,R*)-methylphenidate (1) can be conveniently obtained by means of biocatalytic resolution of a racemic compound of formula 2 (of which one enantiomer is shown, for
15 convenience), using a range of hydrolase enzymes.



Description of the Invention

25 According to the first aspect of this invention, and by appropriate use of partially enantiomerically-enriched salt, crystallisation can be used to give essentially enantiopure *threo*-methylphenidate. The starting material should be enantiomerically enriched above the eutectic point of the *threo*-methylphenidate salt. In the case of *threo*-methylphenidate hydrochloride salt, the eutectic point has been measured to be 25% ee by solubility. That
30 is to say, *threo*-methylphenidate.HCl salt with a composition of enantiomers greater than 25% ee will, by crystallisation, yield enriched material. Thus, by contrast with the crystallisation reported by Patrick *et al*, *supra*, *threo*-methylphenidate salts of significantly

lower enantiomeric purity, in the range 25-95%, preferably 50-95%, and more preferably 70-95%, can be usefully enriched by direct crystallisation. The process of the invention is therefore of considerable utility with a feedstock of *threo*-methylphenidate of moderate enantiomeric purity, for example following classical resolution. Any resolving agent that
5 may be present can be removed, e.g. to a level of 2% w/w or below, e.g. no more than 0.5 or 1% w/w. Preferably, there is no chemical resolving agent, as in bioresolution or asymmetric synthesis. In the latter two cases at least, the feedstock is uncontaminated by resolving agent. For example, the novel crystallisation process can be used in combination with the novel biocatalytic resolution.

10 By way of example, the novel bioresolution encompasses the following embodiments:

(i) where R = Me, enantioselective hydrolysis of unwanted (*S,S*)-methylphenidate (*l-threo*) affords (*S,S*)-ritalinic acid, which is easily separated from unreacted (*R,R*)-methylphenidate by extraction into dilute aqueous alkali.

15 (ii) where R = Me (or another lower alkyl group), enantioselective hydrolysis of (*R,R*)-methylphenidate (*d-threo*) is followed by isolation of (*R,R*)-ritalinic acid and chemical esterification. To maximise atom utilisation, recycling of the unreacted (*S,S*)-methylphenidate (*l-threo*) may be carried out according to the procedure described in WO-A-9728124.

20 (iii) where R = H, enantioselective esterification of (*R,R*)-ritalinic acid affords (*R,R*)-methylphenidate directly.

(iv) where R = H, enantioselective esterification of (*S,S*)-ritalinic acid, is followed by separation from the (*R,R*)-antipode, and chemical esterification of the latter.

25 Compared with classical resolution, the bioresolution process of the present invention provides a number of benefits, including mild reaction conditions (ambient temperature, low environmental impact), cost savings by avoidance of stoichiometric resolving agents, and easier processing (e.g. simple solvent partitioning in selected cases instead of salt cracking).

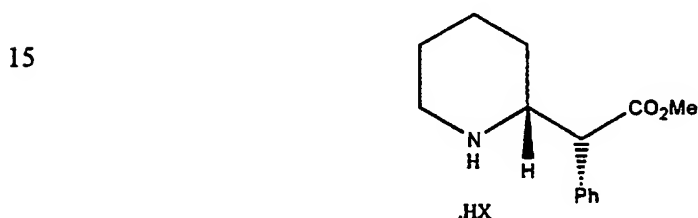
30 As will be apparent from Example 1, suitable biocatalysts can readily be identified. It is preferred that the biocatalyst provides a sufficient degree of optical

enrichment that the desired product can be used effectively, e.g. at least 20%, preferably at least 40%, and more preferably at least 50%, ee, up to substantially single enantiomer product, e.g. at least 80% or 90% ee.

The novel crystallisation process is also useful to enhance the ee of material of high ee, e.g. at least 95% ee, if that has been produced in chemically-pure form, using a more efficient resolving agent for this purpose than 1,1'-binaphthyl-2,2'-diyl hydrogen phosphate. Such processes are described in WO-A-9727176 and WO-A-9732851.

The solvent that is used in the invention can readily be chosen by those of ordinary skill in the art. For example, the solvent should be sufficiently polar, e.g. an alcohol, optionally together with another solvent such as an ether. An aprotic solvent such as acetonitrile or acetone can also be used. A mixture of methanol and TBME is preferred.

The salt used in the invention may have the formula



20 wherein HX is any achiral acid that forms a suitable salt. The suitability of any salt for use in the invention is readily tested in a crystallisation procedure by one of ordinary skill in the art. HX is preferably a hydrohalide, and X is more preferably Br or Cl.

For the purposes of comparison, racemic *dl*-*threo*-methylphenidate.HCl (1.0 g) was suspended in 10 ml of 1:1 methanol:TBME (7.4 g) and stirred at 25°C for 16 hours. 25 The solid material was collected by filtration, washing the reaction vessel with 10 ml TBME. This gave 0.640 g of solid precipitate. The mother liquors were evaporated to dryness to give 0.340 g of a white solid. *dl*-*threo*-methylphenidate.HCl therefore has a solubility of 34 mg per ml of 1:1 MeOH:TBME at 25°C.

This experiment was repeated using 20% ee, 25% ee and single enantiomer *d*- 30 *threo*-methylphenidate.HCl. These and other solubility results, obtained using essentially the same procedure, are reported in Table 1. In the Tables, MPH = *threo*-methylphenidate, PPT = precipitate, and MLS = mother liquor.

Table 1 shows solubility measurements for *threo*-methylphenidate hydrochloride of different enantiomeric composition (racemate, or enriched in the *d* enantiomer), and also demonstrates one embodiment of the present invention, namely the ee enhancement achieved by dissolution of the materials in a 1:1 mixture of methanol:TBME at 25°C, and separation of insoluble material. The point of maximum solubility is at 25% ee, which defines the eutectic composition and the solubility ratio $\alpha = 34.0/17.0 = 2.0$. Enhancement of ee is slight when the initial ee is 30%, increasing to 31.9%, but a progressive enhancement is observed when the initial ee is higher.

Table 1

10	ee MPH.HCl	ee PPT	ee MLS	Solubility (mg/per ml)
	0%	-	-	34.0
	20%	15.9%	25.0%	36.0
	25%	19.9%	24.7%	40.0
	30%	31.9%	22.6%	33.0
15	50%	54.4%	24.3%	27.7
	60%	70.7%	25.1%	26.5
	73%	93.0%	46.0%	25.5
	99%	-	-	17.0

20 In another embodiment of the present invention, the enrichment procedure may also be effected by simply treating a solution of *threo*-methylphenidate free base above the eutectic point (>25% ee) with hydrogen chloride in methanol, and isolating the resultant precipitate. The results of a series of experiments are given in Table 2.

25 Table 2

	ee MPH	ee PPT (% yield)	ee MLS (% yield)
	82% - <i>l-threo</i>	97.0% (65%)	36.9% (35%)
	87% - <i>l-threo</i>	98.0% (69%)	35.7% (23%)
	88% - <i>l-threo</i>	97.8% (78%)	32.1% (21%)
30	91% - <i>d-threo</i>	99.2% (80%)	43.6% (19%)
	94% - <i>d-threo</i>	99.7% (86%)	72.3% (8%)
	95% - <i>d-threo</i>	99.0% (90%)	36.5% (6%)

The following Examples illustrate the present invention more specifically.

Example 1

Suitable enzymes for the bioresolution were identified by the following screening protocol:

- 5 100 mg of racemic *threo*-methylphenidate (free base) was dissolved in 100 mM phosphate buffer adjusted to pH 7. Approximately 50 mg (or equivalent ml) of each candidate enzyme was added and the reactions incubated at 30°C for 24 hours with gentle agitation. For assaying purposes, 40 μ l of the reaction mixture was dispensed into a vial and allowed to evaporate over KOH in a desiccator overnight. The residue
- 10 was then dissolved in 1 ml IPA/2% diethylamine solution and undissolved material removed by centrifugation. The enantiomeric composition of the unreacted *threo*-methylphenidate remaining in solution was analysed by hplc method on the Chirapak AD column using 90:10:0.2 heptane/IPA/diethylamine at 0.5 ml/min and $\lambda=227$ nm. Any ritalinic acid also present in the solution was found not to interfere with the
- 15 detection of the enantiomeric methyl esters.

A representative result was obtained using α -chymotrypsin (Sigma). Its use gave a ratio of enantiomers of unreacted substrate (*SS:RR*) of 79.5:20.5.

Example 2

- d-threo*-methylphenidate.HCl enriched in the *d*-enantiomer (73% ee) (0.950 g) was
- 20 suspended in 10 ml of 1:1 methanol:TBME (7.7 g) and stirred at 25°C for 16 hours. The solid material was collected by filtration, washing the reaction vessel with 10 ml TBME. This gave 0.725 g of solid precipitate, with an enantiomeric excess of 93.0%. The mother liquors were evaporated to dryness to give 0.255 g of a white solid, with an enantiomeric excess of 46.0%. *d-threo*-methylphenidate.HCl (73% ee) therefore has a solubility of 25.5
- 25 mg per ml of 1:1 MeOH:TBME at 25°C.

Example 3

- d-threo*-methylphenidate.HCl enriched in the *d*-enantiomer (50% ee) (1.00 g) was
- suspended in 10 ml of 1:1 methanol:TBME (7.9 g) and stirred at 25°C for 16 hours. The solid material was collected by filtration, washing the reaction vessel with 10 ml TBME.
- 30 This gave 0.710 g of solid precipitate, with an enantiomeric excess of 54.4%. The mother liquors were evaporated to dryness to give 0.277 g of a white solid, with an enantiomeric

excess of 24.3%. *d*-threo-methylphenidate.HCl (50.0% ee) therefore has a solubility of 27.7 mg per ml of 1:1 MeOH:TBME at 25°C.

Example 4

d-threo-methylphenidate.HCl enriched in the *d*-enantiomer (60% ee) (1.00 g) was
5 suspended in 10 ml of 1:1 methanol:TBME (7.7 g) and stirred at 25°C for 16 hours. The solid material was collected by filtration, washing the reaction vessel with 10 ml TBME. This gave 0.710 g of solid precipitate, with an enantiomeric excess of 70.7%. The mother liquors were evaporated to dryness to give 0.265 g of a white solid, with an enantiomeric excess of 25.1%. *d*-threo-methylphenidate.HCl (60% ee) therefore has a solubility of 26.5
10 mg per ml of 1:1 MeOH:TBME at 25°C.

Example 5

d-threo-methylphenidate.HCl enriched in the *d*-enantiomer (30% ee) (1.00 g) was suspended in 10 ml of 1:1 methanol:TBME (7.7 g) and stirred at 25°C for 16 hours. The solid material was collected by filtration, washing the reaction vessel with 10 ml TBME.
15 This gave 0.655 g of solid precipitate, with an enantiomeric excess of 31.9%. The mother liquors were evaporated to dryness to give 0.330 g of a white solid, with an enantiomeric excess of 22.6%. *d*-threo-methylphenidate.HCl (30% ee) therefore has a solubility of 33.0 mg per ml of 1:1 MeOH:TBME at 25°C.

Example 6

20 *l*-threo-methylphenidate enriched in the *l*-enantiomer (88.3% ee) 15.0 g was taken up in 30 ml of methanol, and stirred at 40-50°C whilst bubbling hydrogen chloride gas through the reaction mixture for 10 minutes. The reaction mixture was then heated at reflux for 5 minutes. After this 30 ml TBME was added to the reaction mixture which was cooled over one hour to room temperature, and finally at 0°C for 1 hour. The solid
25 material was collected by filtration, washing the reaction vessel with 30 ml TBME. This gave 13.50 g (77.8%) of solid precipitate, with an enantiomeric excess of 97.8%. The mother liquors were evaporated to dryness to give 3.60 g of a yellow/orange solid (20.7%), with an enantiomeric excess of 32.1%.

Example 7

30 *d*-threo-methylphenidate enriched in the *d*-enantiomer (91.3% ee) 11.50 g was taken up in 23 ml of methanol, and stirred at 40-50°C whilst bubbling hydrogen chloride gas through the reaction mixture for 10 minutes. The reaction mixture was then heated at

reflux for 5 minutes. After this 23 ml TMBE was added to the reaction mixture which was cooled over one hour to room temperature, and finally at 0°C for 1 hour. The solid material was collected by filtration, washing the reaction vessel with 23 ml TMBE. This gave 10.60 g (79.7%) of solid precipitate, with an enantiomeric excess of 99.2%. The mother liquors were evaporated to dryness to give 2.50 g of a white solid (18.8%), with an enantiomeric excess of 43.6%.

In order to demonstrate the broader applicability of the invention, the corresponding hydrobromide salt was prepared. Firstly, *dl-threo*-methylphenidate (0.86 g; 3.71 mmol) and ammonium bromide (0.436 g; 4.45 mmol) were taken up in 10 ml methanol and stirred at 25°C for 10 minutes. The solvent was removed under vacuum, this process being repeated a further two times. The resulting white crystalline material was taken up in 25 ml dichloromethane, and filtered through Celite. This gave 0.97 g of a white solid (83.3%). MP = 205.6°C. IR (KBr) ν_{\max} = 1730 cm⁻¹.

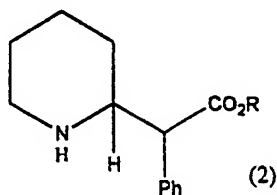
The resultant racemic *dl-threo*-methylphenidate.HBr (0.500 g) was suspended in 5 ml of 1:1 methanol:TBME (3.80 g) and stirred at 25°C for 16 hours. The solid material was collected by filtration. This gave 0.355 g of solid precipitate. The mother liquors were evaporated to dryness to give 0.140 g of a white solid. *dl-threo*-methylphenidate.HBr therefore has a solubility of 28 mg per ml of 1:1 MeOH:TBME at 25°C.

Secondly, *d-threo*-methylphenidate (0.86 g; 3.71 mmol) and ammonium bromide (0.436 g; 4.45 mmol) were taken up in 10 ml of methanol and stirred at 25°C for 10 minutes. The solvent was removed under vacuum, this process being repeated a further two times. The resulting white crystalline material was taken up in 25 ml dichloromethane, and filtered through Celite. This gave 0.75 g of a white solid (64.4%). MP = 222.6°C. IR (KBr) ν_{\max} = 1730 cm⁻¹.

The resultant single enantiomer *d-threo*-methylphenidate.HBr (1.0 g) was suspended in 5 ml of 1:1 methanol:TBME (4.00 g) and stirred at 25°C for 16 hours. The solid material was collected by filtration. This gave 0.430 g of solid precipitate. The mother liquors were evaporated to dryness to give 0.070 g of a white solid. *d-threo*-methylphenidate.HBr therefore has a solubility of 14.0 mg per ml of 1:1 MeOH:TBME at 25°C.

CLAIMS

1. A process for increasing the enantiomeric excess of an enantiomerically- enriched mixture of enantiomers of an acid addition salt of *threo*-methylphenidate, wherein said acid is achiral, which comprises crystallisation from, or partial dissolution in, a solvent; and, if
5 necessary, removing any resolving agent that may be present.
2. A process according to claim 1, wherein crystallisation follows dissolution of the pre-formed acid addition salt in a solvent.
3. A process according to claim 1, wherein crystallisation follows addition of the acid to a solution of *threo*-methylphenidate free base.
- 10 4. A process according to any preceding claim, wherein, prior to crystallisation of the acid addition salt, the initial ee is at least 25% ee.
5. A process according to claim 4, wherein the initial ee is 25 to 95%.
6. A process according to claim 4, wherein the initial ee is 50 to 95%.
7. A process according to claim 4, wherein the initial ee is 70 to 95%.
- 15 8. A process according to any preceding claim, wherein the mixture of enantiomers contains less than 2% w/w resolving agent.
9. A process according to any preceding claim, wherein the acid is a hydrohalide.
10. A process according to claim 9, wherein the acid is HCl.
11. A process according to claim 9, wherein the acid is HBr.
- 20 12. A process according to any preceding claim, for the preparation of *d-threo* methylphenidate hydrochloride of enantiomeric purity in excess of 98% ee.
13. A process according to any preceding claim, which follows classical resolution and, optionally, removal of resolving agent.
14. A process according to any of claims 1 to 12, which follows asymmetric synthesis.
- 25 15. A process according to any of claims 1 to 12, which follows bioresolution.
16. A process for preparing enantiomerically-enriched *d,threo*-methylphenidate, which comprises biocatalytic resolution of a racemic compound of the formula



wherein the relative stereochemistry is *threo*, and R is H or methyl.

17. A process according to claim 16, wherein racemic *threo*-methylphenidate is subjected to hydrolysis in the presence of an enzyme that displays enantioselectivity.
18. A process according to claim 16, wherein racemic ritalinic acid is subjected to
5 esterification in the presence of an enzyme that displays enantioselectivity.
19. A process according to claim 17 or claim 18, which additionally comprises conventional chemical esterification of (*R,R*)-ritalinic acid.
20. A process according to any of claims 17 to 19, wherein the enzyme is α -chymotrypsin (bovine pancreas).
- 10 21. A process according to any of claims 16 to 20, wherein the enzyme is in immobilised form.
22. A process according to claim 15, wherein the bioresolution is a process according to any of claims 16 to 21.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 97/03418

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D211/34 A61K31/445

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PATRICK K S ET AL: "PHARMACOLOGY OF THE ENANTIOMERS OF THREO-METHYLPHENIDATE" JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 241, no. 1, April 1987, pages 152-158, XP000602302 cited in the application	1-22
A	EP 0 687 736 A (BASF AG) 20 December 1995 see abstract	16



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

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Date of the actual completion of the international search

16 March 1998

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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